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THE ACTION OF CHLOROFORM UPON THE HEART AND ARTERIES.

BY

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XII.—The Action of Chloroform upon the Heart and Arteries. By E. A. Schäfer, F.R.S., and H. J. Scharlieb, M.D., C.M.G. (*From the Physiological Laboratory of the University of Edinburgh.*)

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The original design of this research was to determine whether the extract of suprarenal medulla (or its active principle) has the power of antagonising the effects of an overdose of chloroform upon the heart and arterial system. Incidentally the research became extended so as to cover the action of certain other antagonising agents. It further appeared necessary, as the investigation proceeded, to subject the action of chloroform upon the vascular system to renewed study. For although, as the result of numerous recent researches, physiologists are in agreement regarding the general effect of the drug upon the heart, there yet remain various points requiring elucidation both as regards its effect on the heart and on the arteries.

Effect of Chloroform upon the Arteries.

Singularly little is precisely known as to the effect of the drug upon the arterial system. The most generally received opinion has been that adopted by Bowditch and Minot * to the effect that chloroform exerts, besides a specific action on the heart, a paralysing influence upon the whole vasomotor system, and that the fall of blood-pressure which accompanies its administration is due as well to the dilatation of vessels as to the effect which it produces upon the cardiac musculature. On the other hand, Arloing,† as the result of observations on the rate of flow through the carotid, made by means of the hæmadromograph, inferred that a constriction of arterioles is produced by the drug. Dastre‡ came to the same conclusion, and referred to it the pallor of the face which is seen in chloroform administration. But it is obvious that a diminution of rate in the carotid might be caused by dilatation of vessels in the splanchnic area, so that these observations cannot be regarded as conclusive. Gaskell and Shore,§ in their cross-circulation experiments, obtained distinct evidence of stimulation of the vasomotor centre; constriction of arterioles and rise of blood-pressure occurring as the result of the action of the drug upon the medulla oblongata. Roy and Sherrington ‖ inferred that constriction of cerebral vessels is produced by chloro-

* *Boston Med. and Surg. Jour.*, 1874. *Cf.* Leonard Hill, *Brit. Med. Jour.*, April 1897.
† Thèse, Paris, 1879.
‡ *Les Anesthétiques*, 1890.
§ *Brit. Med. Jour.*, 1893, vol. i.
‖ *Jour. Physiol.*, vol. xi. p. 97, 1890.

form, while HÜRTHLE* found evidence of dilatation of these vessels, followed by constriction. NEWMAN† observed constriction of pulmonary capillaries in the frog as the result of chloroform inhalation. SHERRINGTON and SOWTON,‡ working with the isolated mammalian heart perfused with Ringer's solution by Langendorff's method, observed a diminished flow of the perfusion fluid when chloroform was added to it; this they were inclined to ascribe to a contraction of coronary vessels under its influence. C. J. MARTIN§ has suggested that this diminution of flow through the coronary vessels may be accounted for, without the necessity of assuming constriction of those vessels, by the fact that a diminished action of the cardiac musculature, such as chloroform produces, may tend by itself to diminish the rate of circulation through its vessels. To this we may add that in a heart which is separated from its surroundings and fed by the perfusion of fluid under pressure into the root of the aorta, in which therefore the mechanical conditions are very different from those which obtain normally, the aortic valves do not necessarily act efficiently, but often permit of some passage of fluid into the cavity of the left ventricle, and through this into the left auricle, and so out by the cut pulmonary veins; and the extent of this valvular defect with the consequent leakage will vary with the condition of tone of the heart and the force of its contractions.

Opinions on this subject being thus divided, it appeared important in the first instance to determine what is precisely the action of chloroform upon the arterial system. The method which we have used for this purpose is the classical one of perfusing the vessels with blood or saline fluid containing the drug in solution. The chloroform used for this purpose and in most of our experiments has been Duncan & Flockhart's, sp.gr. 1·49. The result of our preliminary experiments‖ showed that a solution containing from 1 gramme to 5 grammes of chloroform to the litre of circulating fluid produces a marked constriction of the frog's arterioles, and that this constriction is apparent whether the medulla oblongata and spinal cord are left intact or destroyed. These observations established the fact that for high percentages of chloroform (5 grammes per litre is approximately a saturated solution, and 1 gramme per litre is therefore one-fifth saturated) there is a pronounced excitation by the drug of the musculature of the arterioles—whether operating directly or through the vasomotor nerve-endings, our preliminary experiments did not decide—which may contract under its influence to such an extent as almost to arrest the flow of circulating fluid.

Since the publication of these preliminary results, C. J. MARTIN,§ in confirmation of earlier experiments in conjunction with EMBLEY,¶ has made observations upon the mammalian kidney by the plethysmographic method which appear to indicate that in dilute solution—the actual dosage was not determined, but the perfusing fluid (blood) was first passed through the lungs, into which a mixture of air and chloroform vapour was pumped—chloroform has the effect upon the blood-vessels ascribed

* *Pflüger's Arch.*, vol. xliv. p. 596, 1889.
† *Jour. Anat. and Phys.* vol. xiv., 1879, p. 495.
‡ *Thompson-Yates Laboratories Reports*, 1903, vol. v.
§ Private communication.
‖ Communication to the Physiol. Soc.; *Jour. Phys.*, vol. xxix., 1903.
¶ *Brit. Med. Jour.*, April 1902. *Lancet*, 1902.

to it by Bowditch and Minot, viz., that of producing dilatation. In repeating and extending our experiments we have therefore included the effect of the perfusion of mammalian organs with various strengths of chloroform dissolved in Ringer's solution.

Perfusion of Frog Vessels with Chloroform dissolved in Ringer's Solution.

The Ringer's fluid used consisted of NaCl, 6 grammes; $CaCl_2$, 0·1 gramme; KCl, 0·075 gramme; $NaHCO_3$, 0·1 gramme per litre. The chloroform was either dissolved in this solution in proportion determined by weight, or some of the fluid was saturated by being shaken up with and kept over an excess of chloroform, and was assumed to contain 1 part chloroform to 200 Ringer, this being the amount water will take up at the ordinary temperature of the air (15° C.). This saturated solution was mixed with varying proportions of normal Ringer. A fine cannula having been tied into the bulbus aortæ of the frog (*R. esculenta* or *R. temporaria*), the fluid was allowed to pass by gravity, at a pressure varying in different experiments from 50 mm. to 150 mm. of water, through the vascular system, and to drip from the extremities of the toes. In our earlier experiments the mode of determining the rate of flow was to count the number of drops per minute; but this method, although serving to indicate any differences of vascular calibre which are marked, is not sufficiently accurate for slight variations, since the size of the drops is liable to vary somewhat with differences of surface tension of the fluid, and the amount of dissolved chloroform or of intermixed blood and lymph may affect its surface tension. In all later experiments, therefore, the amount of fluid perfusing in a given time was accurately measured. Only the results thus obtained are included in this communication.

The result of these perfusion experiments with Ringer's fluid containing dissolved chloroform may be shortly stated as follows:—

With the strongest solutions, *i.e.*, from saturated (1 in 200) down to solutions containing 1 in 500, a very marked constriction of the arterioles is the result of perfusing with chloroform-Ringer, so that the flow of the perfusing fluid becomes very slow, and may almost cease. With increase of dilution the amount of constriction, as registered by rate of flow, becomes less; but although very slight when the dilution is considerable, we have been able to substantiate constriction with solutions as weak as 1 in 20,000. On the other hand, no solution of any strength when perfused through the frog's vessels has given evidence of dilatation of arterioles, the weaker solutions having simply shown themselves inert. If for the chloroform-Ringer which has been passed for some minutes through the vessels, and has produced the diminutions of flow above indicated, normal Ringer be now substituted, the flow again becomes more rapid, but the original rate is rarely again obtained; in fact, after the chloroform solution has been in action for some minutes, even if the strength of the solution be such as to be insufficient to cause actual constriction of arterioles, there is a tendency towards a gradual diminution in the rate of flow, which appears to be caused by œdema of

the tissues; the effect of the chloroform solution on the endothelium of the vessels being such as to render the capillaries more permeable to saline solution.

The following experiment will serve as an example of the results obtained with weak solutions of chloroform in Ringer's solution. The numbers represent the amount flowing through the vessels in equal periods of time.

Immediately before chloroform perfusion		28·5 c.c.
During perfusion of fluid containing 1 part chloroform in 20,000		22·5 ,,
Immediately after perfusion of chloroform-Ringer	1st period	17·5 ,,
	2nd ,,	21 ,,
	3rd ,,	25 ,,

Perfusion of Mammalian Vessels with Chloroform dissolved in Ringer's Fluid.

The kidney, leg, and heart of the cat, rabbit, or dog were employed, and the method of perfusion was the same as for the frog, except that the head of pressure was higher (80 to 100 mm. Hg.). The Ringer solution had the composition: NaCl, 9 grammes; $CaCl_2$, 0·24 gramme; KCl, 0·42 gramme; $NaHCO_3$, 0·1 gramme; distilled water, 1 litre, and was warmed to 38° C. by being passed through a glass spiral contained in a water-bath before being conducted to the organ to be perfused, which was itself also kept in a warm chamber at the same temperature. The perfused fluid was either collected in a graduated measure and the amount flowing in a given time recorded, or it was caused to work an automatic "tilter," so arranged that every 7 c.c. of fluid produced a see-saw of the tilter, and this was recorded by a magnetic signal. In some experiments Ringer's solution, containing a known percentage of chloroform, was, after the normal record of flow had been obtained, allowed to pass for a certain time through the vessels in place of the ordinary Ringer, and was then again replaced by ordinary Ringer, the rate being recorded before, during, and after the passage. In other experiments a chloroform-Ringer of known strength was injected by a fine hypodermic needle through the indiarubber supply-tube of the perfusion apparatus, so as to mix with the inflowing normal Ringer. The amount of dilution of the chloroform-Ringer so perfused was calculated from the amount of fluid flowing through the kidney during the actual time occupied by the injection. This method has the advantages (1) that the chloroform solution only acts for a short time upon the kidney vessels, and is less liable to cause a permanently deleterious effect; and (2) that the conditions of flow are maintained the same throughout, for if the injection is performed very gradually, no perceptible increase of pressure is caused by it. (It is scarcely possible to change the flow from one vessel to another, as in the ordinary method of testing perfusion, without causing a temporary effect of some kind upon the pressure of the perfusing fluid.)

The results yielded by these methods show that in mammalian as in frog's vessels the effect of chloroform solutions of a certain strength is to cause marked constriction of the arterioles and consequent diminution in the rate of flow of the perfusing liquid. If the flow lasts for a short time only, the rate is soon recovered, but prolonged perfusion

—even with (so-called) normal Ringer, and much more with Ringer containing chloroform—is accompanied by œdema and a consequent permanent diminution in rate of flow.

Kidney.—The strengths of solution which produce constriction in the vessels of the kidney are from saturated (1 in 200) to 1 in 1000 (perhaps somewhat more dilute). But whereas, in the entire frog, solutions weaker than those which cause constriction do not produce dilatation, and have no apparent effect apart from the gradual œdema which results from prolonged action, in the mammalian kidney the effect of weaker solutions is, as C. J. Martin has stated, to cause dilatation. This result has been obtained with solutions of from 1 to 1500 to 1 in 20,000 (in one instance); weaker solutions gave no result.

Coronary Vessels.—In employing the heart we have always taken the precaution of tying the pulmonary veins, to prevent loss of circulating fluid by regurgitation past the aortic and mitral valves. The effect of chloroform upon the coronary arteries is to produce constriction in all strengths from saturated to 1 in 10,000. The stronger solutions of chloroform cause so marked a diminution of the rate through the coronary vessels as to almost arrest the flow of fluid; and this is not due to arrested cardiac action, for on substituting normal Ringer for chloroform-Ringer the rate of flow returns to normal long before the action of the heart recommences. With weaker solutions the effect is also to produce diminished flow, and at no condition of dilution have we obtained evidence of dilatation of vessels.

Limbs.—For this purpose the hind limbs of the rabbit and cat have been used. The results are precisely the same as in the case of the coronary arteries of the mammal and the systemic arteries of the frog. Evidence of constriction has been obtained with all strengths from 1 in 200 (which arrests the flow altogether) to 1 in 10,000 (which causes a slight diminution). More dilute solutions are inactive; we have obtained no evidence of dilatation in these vessels.

The following may serve as examples of the results:—

Kidney of Rabbit:

Amount flowing	before	chloroform perfusion		42 c.c.
,, ,,	during	,, ,,	(1 in 1500 Ringer)	49 ,,
,, ,,	after	,, ,,		35 ,,

The same Kidney, later:

Amount flowing	before	chloroform perfusion		39 c.c.
,, ,,	during	,, ,,	(1 in 700)	17·5 ,,

Kidneys of Kitten:

Amount flowing	before	chloroform perfusion		57 c.c.
,, ,,	during	,, ,,	(1 in 20,000)	60 ,,
,, ,,	after	,, ,,		62 ,,

In this and the next experiment, as the increase was progressive and there was no return towards normal, it is possible that the increase of rate may not have been due to the chloroform. But it is clear that the drug has not caused constriction of the kidney vessels.

The same Kidneys, later:

Amount flowing before chloroform perfusion					64 c.c.
,,	,,	during	,,	(1 in 5000)	67 ,,
,,	,,	during	,,	(1 in 2000)	70 ,,

Subsequent perfusion with suprarenal produced strong constriction, showing that the arterioles were still active.

The effects of stronger and weaker solutions upon the kidney vessels is also well illustrated in the accompanying tracings, which show (in fig. 1) the effect (marked constriction of vessels with rise of pressure

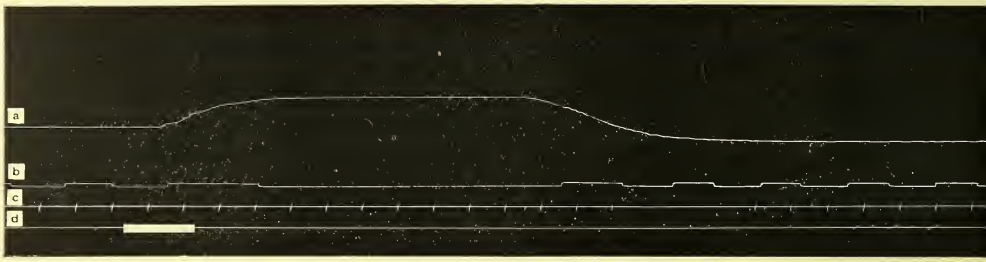

FIG. 1.—Perfusion of rabbit's kidney with Ringer's solution. At the time marked by the signal 4 c.c. of the same solution, containing 0·5 per cent. of chloroform, and at the same temperature, was slowly injected into the supply tube. The mixture of this solution with that passing through the tube at the time gave a fluid containing 0·2 per cent. (1 in 500) actually perfused. Notice the rise of pressure due to constriction of the bloodvessels, followed after the passage of the fluid by a dilatation; also the great diminution in outflow, followed by a slight increase.

a, Register of mercury manometer; *b*, movements of "see-saw," registered by air transmission: each up or down movement represents 7 c.c. of fluid discharged; *c*, time in 10 secs.; *d*, signal line and pressure abscissa.

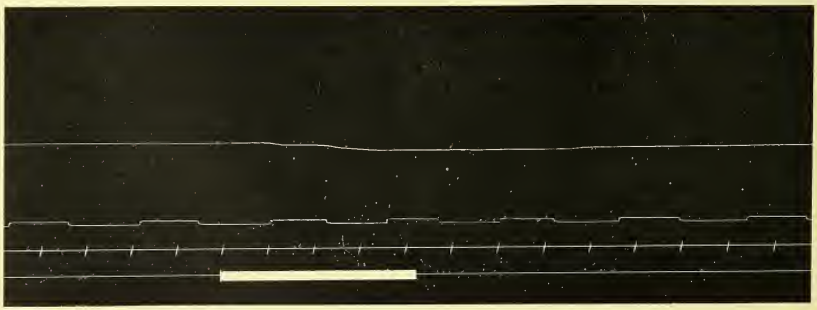

FIG. 2.—Tracing similar to that shown in fig. 1, but with injection of 4 c.c. of 1 in 1000 chloroform, and actual perfusion of 1 in 6000. Notice the fall of pressure and the increase in rate of discharge, indicating dilatation of arteries.

and great diminution of flow) of perfusing a solution of Ringer containing 1 in 500 chloroform; and (in fig. 2) the effect (dilatation of vessels with fall of manometric pressure, and increase of rate of flow) of passing a solution containing 1 in 6000 through the kidney.

Heart of Cat:

Amount flowing through coronary system before chloroform					44 c.c.
,,	,,	,,	,,	during ,, (1 in 10,000)	41·5 ,,
,,	,,	,,	,,	after ,,	44 ,,

Another Heart:

Amount flowing through coronary system	before chloroform	45 c.c.
,, ,, ,, ,, ,,	during ,, (1 in 4000)	32 ,,
,, ,, ,, ,, ,,	after ,,	42 ,,

Heart of Rabbit:

Amount flowing through coronary system	before chloroform	58 c.c.
,, ,, ,, ,, ,,	during ,, (1 in 1500)	40 ,,
,, ,, ,, ,, ,,	after ,,	48 ,,

The same Heart, later:

Amount flowing through coronary system	before chloroform	48 c.c.
,, ,, ,, ,, ,,	during ,, (1 in 1000)	34 ,,
,, ,, ,, ,, ,,	after ,,	42 ,,

The tracing shown in fig. 3 gives an illustration of the effect produced upon the heart by a still stronger chloroform solution, the rate of perfusion falling during the passage of the chloroform from 21 c.c. per minute to 5 c.c. per minute, and gradually recovering as the chloroform was washed away. It will be noticed that the recovery of the vessels appears before the contractions of the heart reappear. It can also be seen that the latency of the arterial contraction is longer than that of the heart paralysis which the chloroform produces.

FIG. 3.—Effect of perfusing 20 c.c. of chloroform-Ringer (= 1 in 500) through the coronary vessels of the rabbit.

a, tracing of manometer connected with supply cannula; *b*, register of flow from coronary veins: each interval represents 7 c.c.; *c*, time in minutes; *d*, signal marking period of injection into supply tube.

Note the diminution in rate of flow, and subsequent commencing recovery although the heart remains in a condition of arrest. The rate of movement of the paper is too slow for the individual heart-beats to be seen on the manometer tracing.

Hind Limbs of Rabbit:

Amount flowing through limbs	before chloroform	86 c.c.
,, ,, ,, ,,	during ,, (1 in 10,000)	77 ,,
,, ,, ,, ,,	after ,,	84 ,,

Hind Limb of Rabbit:

Amount flowing through limb	before chloroform	44 c.c.
,, ,, ,, ,,	after passage of 10 c.c. of 1 in 2000 chloroform-Ringer	39 ,,
,, ,, ,, ,,	in subsequent period	42 ,,

These observations show that the kidney differs from the other organs investigated in the fact that the more dilute solutions of chloroform produce an increased flow through the kidney vessels, whereas in the other organs (heart, limbs) the effect of the drug is always in the direction of vasoconstriction. The difference is a remarkable one; but without discussing it at greater length, we may point out that dilatation of the renal vessels is the normal response of the organ to all but a very few excitants, whereas the normal response of most vessels to an excitation is contraction, and it is possible therefore that the explanation is connected with this difference of "habit" of the kidney vessels as compared with the systemic vessels generally.

The action of chloroform upon the vessels when perfused through the isolated organs is a direct action upon the muscular tissue, and not, as in the case of suprarenal extract, upon the terminal apparatus of the vasomotor nerves. This is shown by the fact that apocodeine, which in sufficient dose abolishes the effect of adrenalin,* does not abolish the effect of chloroform in producing vasoconstriction.

The following experiment may be quoted in illustration of this statement:—

Hind Limb of Rabbit.—Perfusion with 1 in 2000 chloroform reduced the rate of flow during each period of time from 44 c.c. to 39 c.c. After recovery, perfusion with 0·0001 gramme hemisine (adrenalin) added to the normal Ringer brought it down to 10 c.c. After recovery, perfusion with Ringer solution, containing 0·0001 gramme hemisine and 0·0075 gramme apocodeine, caused only a slight reduction, soon disappearing. After recovery, admixture with the perfusing fluid of 10 c.c. of chloroform-Ringer (= 1 in 500), containing 0·02 gramme apocodeine, caused an almost complete arrest of flow during several minutes. Fig. 4 is a graphic record of this experiment.

In all cases the drugs were injected into the tube which supplied the normal Ringer, and the solution became mixed with a certain proportion of this, and warmed to the same temperature by passing through the glass spiral before reaching the organ which was perfused.

As a further proof that chloroform acts upon the muscular tissue of the arterioles in

Fig. 4.—Effect of injecting 10 c.c. of chloroform-Ringer (=1 in 500) containing 0·02 gramme apocodeine through the vessels of the hind limb of the rabbit.

a, *b*, *c*, *d* as in fig. 3. The tracing is taken on a more slowly moving surface than that in fig. 3. The initial pressure of the perfusion fluid was lower in this experiment than in the experiment shown in fig. 3, and the supply less free: this, as well as more complete constriction of the arterioles, accounts for the fact that the manometer tracing is much affected in the one case and scarcely at all in the other.

producing contraction may be adduced the observation that its action can be got after the neuro-muscular end-apparatus has lost its irritability. Thus in the kidney of a rabbit, which had been killed three hours previously and in which the injection of 0·0003 gramme hemisine (adrenalin) produced no effect whatever upon the rate of flow, injection of 20 c.c. of 1 in 200 chloroform-Ringer into the supply-tube reduced the rate from 56 c.c. to 28 c.c.

All recent observers are agreed that the fall of blood-pressure which is caused by chloroform is essentially due to its effect upon the heart muscle, the action of which is weakened and eventually paralysed by the drug. Martin and Embley are, as we have seen, inclined to ascribe the fall—in a minor degree—partly to the dilatation which may be produced in the peripheral vessels by small doses of the drug. But since Gaskell and Shore have shown that the effect of chloroform is to excite the vasomotor centre in the medulla oblongata, and thus to cause contraction of the

* Dixon, *Jour. Phys.*, vol. xxx., p. 97, 1904. Also Brodie and Dixon, *ibid.*, p. 476.

arterioles—an observation which MARTIN and EMBLEY themselves confirm—it is extremely improbable that, while this centre is in action, the dilating effect, if really existent, upon the periphery would be at all apparent. On the other hand, with stronger dosage of chloroform, the direct effect upon the arterioles is always one of constriction. It follows, therefore, that at the beginning of a chloroform inhalation there will be a tendency to counteract the fall of blood-pressure due to heart weakening, by

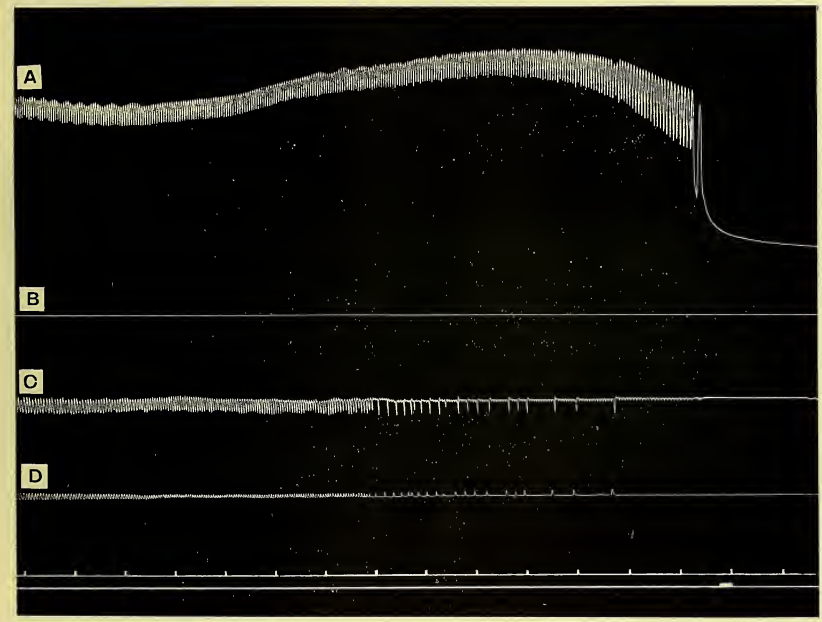

FIG. 5.—End of a fatal chloroform inhalation. Dog, 6570 g. Inhalation through trachea tube of air strongly charged with chloroform vapour.

A, blood-pressure curve; B, line 1 centimetre below zero of blood-pressure; C, costal respiration (the small waves upon this are heart movements); D, diaphragmatic respiration. Time in 10 secs. The signal marks the removal of chloroform. Respirations ceased 20 secs. before the heart. The subterminal rise in blood-pressure which sometimes occurs is shown in this tracing. The increase in size of the manometer excursions is due to a gradual slowing of the heart rhythm, and does not represent an increase of force of the contractions.

excitation of the vasomotor centre, and later on, while this may still be active,* a similar tendency to counteract the fall by direct excitation of the peripheral arterioles. As a general rule, the action of the drug upon the heart is so marked as to more than counter-balance the arterial constriction, however produced. But in certain cases a

* Reflex constriction of bloodvessels can be obtained, on stimulating an afferent nerve, even if chloroform anæsthesia is very pronounced, showing that even in deep anæsthesia the vasomotor centre is still active, although its activity is no doubt lessened. *Cf.* BOWDITCH and MINOT, *op. cit.* Further, chloroform does not diminish the excitability of the peripheral vasomotor nerves (SCHEINENSSON, *Centralbl. f. d. med. Wiss.*, 1869, p. 105).

brief rise of pressure at the beginning of an experiment is sufficiently manifest, and in others again there is apparent, even when the respirations are maintained, a rise towards the end of the experiment. Since in these cases asphyxia is eliminated, and the heart is probably not beating more but less strongly, such a subterminal rise can only be ascribed to the excitatory action of the drug upon the vasomotor centre, or directly upon the arterioles. It is exemplified in fig. 5, which shows the tracing from the latter half of an acute chloroform poisoning, terminating by a slowing and arrest of the respirations, followed after a few seconds, suddenly, by complete arrest of the heart. In this tracing it will be observed that long before the failure of the respiration begins to show itself there is a decided tendency to rise on the part of the arterial pressure, although the heart at this time is not beating more but rather less strongly (the increase in size of

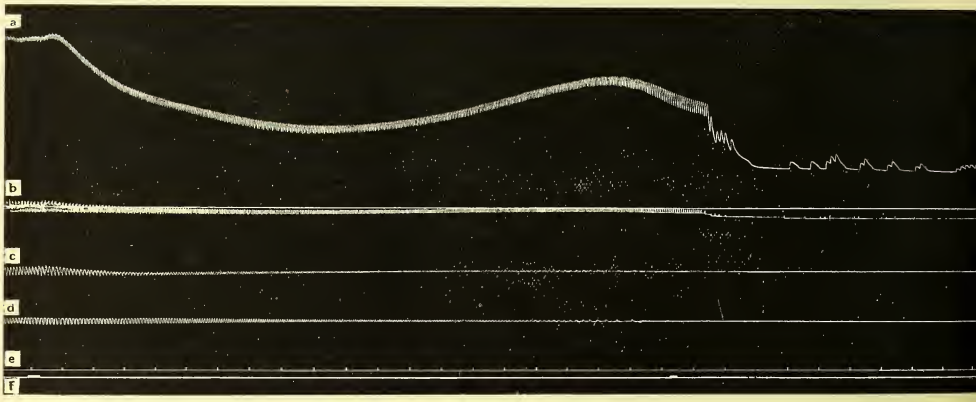

FIG. 6.—Tracing (dog) showing marked secondary rise of blood-pressure during chloroform inhalation, probably due to early failure of respiration. The chloroform was administered between the two marks on the signal line. Notice the cardiac inhibition, which in this case is more gradually developed than usual, and the subsequent escape of the ventricle, which continued to beat feebly for a minute or two, but with hardly any rise of blood-pressure. Artificial respiration by pump commenced 10 minutes after natural respiration had ceased, failed to effect recovery.

a, blood-pressure; *b*, tracing from needle passed through chest wall into ventricle; *c*, thoracic movements; *d*, diaphragmatic respirations; *e*, time in 10 seconds; *f*, signal. The horizontal line at *b* is 10 mm. below the abscissa of blood-pressure.

the arterial pulsations seen near the end is a result of slowing of the cardiac rhythm). This rise of pressure therefore must be due to arterial constriction caused by the drug. The chloroform was given as concentrated vapour, producing abolition of corneal reflex in one minute and death in about four minutes; but how far the constriction was due to direct action upon the arterioles, and how far to an action upon the vasomotor centre, the experiment does not determine. The continuation of the rise in the tracing may perhaps be ascribed to a condition produced by the commencing failure of respiration, the vasomotor centre being stimulated by the venous blood; especially as it is accompanied by a certain amount of cardiac inhibition. Such asphyxial rise may be very marked

when the respirations become shallow early in the administration, as is shown strikingly in the tracing given in fig. 6.

While cases showing such a marked subterminal rise are uncommon, it is not unusual to find a subterminal arrest of the fall of blood-pressure, so that the curve remains for a minute or two at the same level, or shows a more gradual fall than immediately before and immediately after. Such arrest of fall, when unaccompanied by failure of respiration, may also be explained by the constricting action of the drug on the arterioles, acting either through the vasomotor centre or directly. This con-

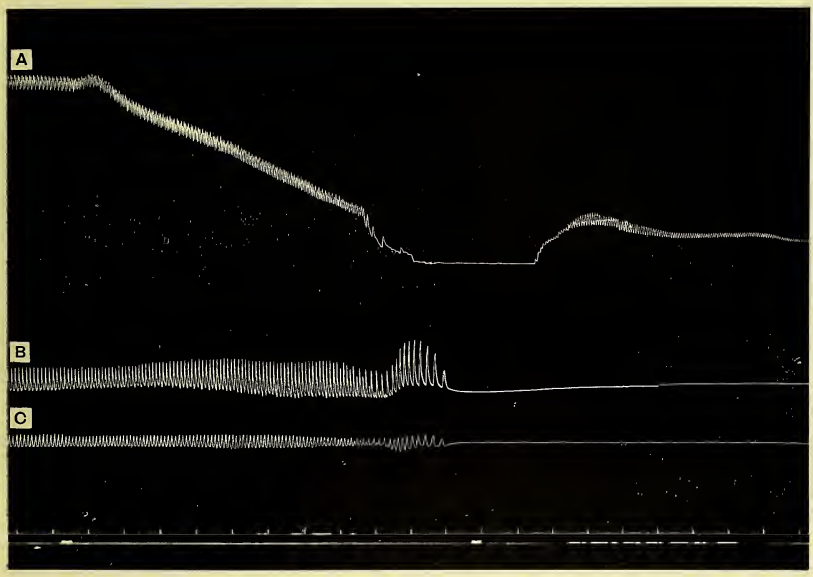

FIG. 7.—Dog, weight 7000 g. Effect of inhalation through trachea tube of air nearly saturated with chloroform vapour.

The uppermost tracing (A) is that of the blood-pressure; the second tracing (B) is costal respiration; the third (C) abdominal respiration; the fourth, time in 10 seconds; and the fifth, the signal marking when chloroform was admitted and stopped.

In this experiment the heart failed before the respiration, and about 30 seconds later showed spontaneous recovery, which was, however, only temporary. There was no recovery of respiration.

striction, although insufficient entirely to compensate for the continual and gradual weakening and slowing of the heart which is going on the whole time, interferes with the continuous and uniform fall of pressure, which would otherwise show itself. At a much later stage the ventricular contractions, although greatly weakened, produce large fluctuations of pressure in the arterial system, which is then comparatively empty, owing to the accumulation of blood in the great veins and in the dilated heart cavities.

Effect of Chloroform upon the Heart.

Our experiments abundantly illustrate the fact, which is now unreservedly conceded, that of all ordinary anæsthetics chloroform is the one which produces the most deleterious effect upon both heart and respirations. Nothing is more striking than the comparison of tracings from chloroform experiments, such as those shown in figs. 5, 6, and 7, with one in which ether is the anæsthetic agent (fig. 8). We have further

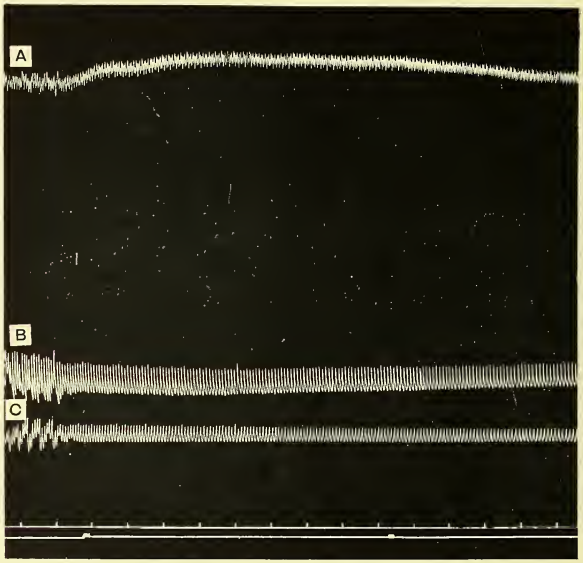

Fig. 8.—This tracing was taken from the same animal as fig. 7, and immediately before it. Air saturated or nearly saturated with ether was inhaled through the trachea tube, between the two points marked by the signal. Previously to this the dog was very lightly anæsthetised with chloroform, corneal reflex being present. Compare the effect of ether upon the blood-pressure and respiration with chloroform, in these tracings.

investigated the action of chloroform upon the heart *in situ* with the chest opened, after the method used by M'William;* and also after removal of the organ from the body, with the coronary vessels perfused by Langendorff's method.†

In confirmation of previous observers, we find that the effect upon the organ when its nervous connections are severed, or when the activity of the vagus is abolished by atropine (fig. 9), is to produce a gradual weakening of the contractions (without any marked slowing, although this may appear towards the end of a fatal experiment)

* *Jour. Phys.*, vol. xiii. p. 860, 1892. † *Pflüger's Arch*, vol. lxi. p. 291, 1895.

affecting both auricles and ventricles; but the former are affected much more than the latter. This is also the case when the cardio-inhibitory centre is reflexly stimulated, even in presence of atropine (fig. 10). On the other hand, when the nervous connections are intact, the administration of a strong dose of chloroform not only greatly weakens the force of the cardiac contractions, and thereby causes a marked and progressive fall of blood-pressure, but often, after a primary acceleration, produces gradual slowing of the rhythm, and this is frequently followed by abrupt and complete cardiac arrest (figs. 6 and 7). The abrupt cessation of contraction may affect both auricles and ventricles simultaneously, or the auricles may first stop; the ventricles, either at once or after a

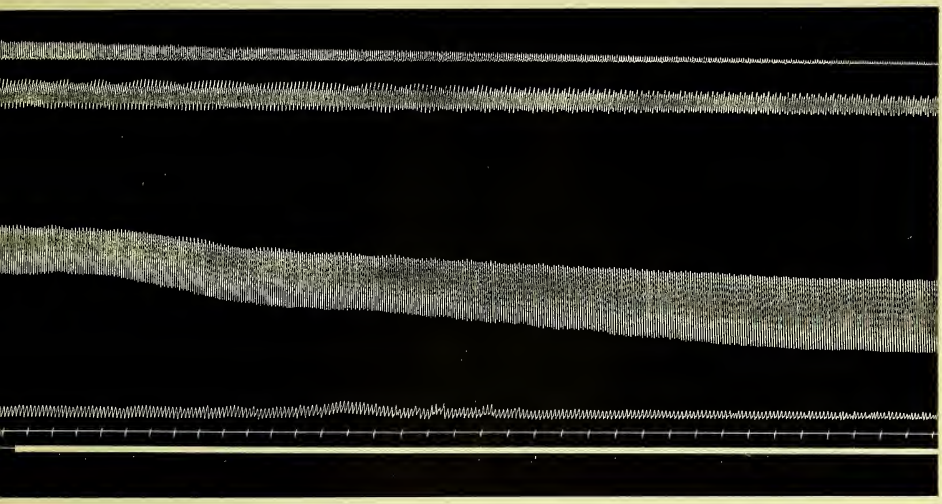

Fig. 9.—Dog, weighing about 10 kilos. The animal had received some 3 hours previously ·00054 gramme ($\frac{1}{120}$ gr.) atropine sulphate administered hypodermically. The effect of this was to abolish arrest of the heart on stimulation of the cardio-inhibitory centre (see fig. 10), whilst permitting a diminution in force of the beats, especially of the auricle. It will be seen from these tracings that exactly the same effect is produced in an animal under the influence of atropine by chloroform alone in strong dose as is caused by reflex excitation of the cardio-inhibitory centre, except that the result is attained more gradually.

a, auricular tracing; *b*, ventricular tracing; *c*, blood-pressure (femoral); *d*, respiratory movements of the thorax, which are continued in spite of the fact that artificial respiration is carried on by perflation; *e*, time in 10 seconds; *f*, signal.

short period of arrest, resuming their action with a rhythm of their own (figs. 6, 7, and 11).

The effect entirely resembles that produced by vagal excitation, with the exception that vagal excitation does not, as a rule, by itself produce permanent arrest of cardiac action. But at a certain stage of chloroform anæsthesia the arrest produced by artificial excitation of the vagus may be permanent, or so prolonged as to lead to death. The cessation of the heart's action brings the blood-pressure to zero, and by arresting the

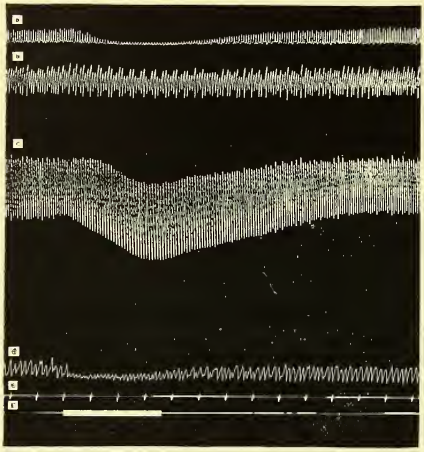

FIG. 10.—Testing of cardiac centre by stimulation of central end of one vagus—the other being intact—in the dog from which the tracing given in fig. 9 was taken, and immediately previous to that tracing.

a, *b*, *c*, *d*, *e*, *f* as before. Notice, as with chloroform, the great diminution in force of the auricular beats, but without arrest or slowing, the diminution in force of the ventricular beats being hardly perceptible. The fall in blood-pressure may be in part due to depressor action, but a similar fall was obtained by stimulation of the peripheral cut vagus.

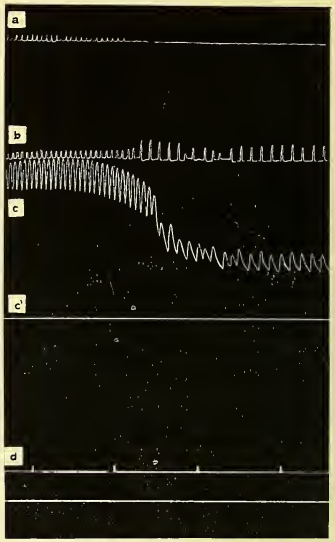

FIG. 11.—Chloroform inhalation. Showing cessation of auricle before ventricle, the latter then assuming its independent rhythm, with larger excursions.

a, auricle; *b*, ventricle; *c*, blood-pressure (the alignment of this pen is a little in advance of the others); c^1, zero of blood-pressure; *d*, time in 10 seconds. Artificial respiration by perflation.

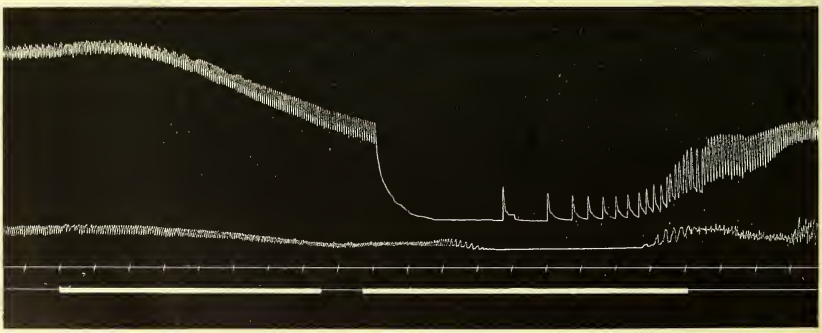

FIG. 12.—Effect of excitation (with coil 100) of the peripheral vagus (second signal) during moderately deep chloroform anæsthesia, strong chloroform vapour having just previously been administered during $1\frac{1}{2}$ minutes (first signal). The result is seen to be an immediate heart arrest, with the blood-pressure falling to zero; the respirations cease 30 seconds after the heart has stopped, but are only gradually arrested. In this case the heart (ventricle?) begins to escape from the arrest after 40 seconds, beating at first very slowly, but after a minute faster: as the heart recovers, the respirations are also renewed.

circulation causes also a failure of the respiratory centre. This cause of respiratory failure has been clearly demonstrated by EMBLEY.*

The complete similarity between the tracings obtained under the influence of chloroform alone on the one hand (when a concentrated vapour is inhaled), and of

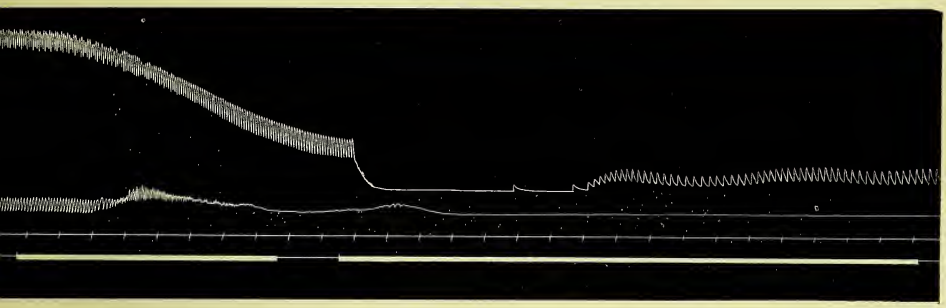

FIG. 13.—Tracing showing the effect of moderate vagus stimulation (coil 100) during deeper chloroform anæsthesia. In this case the excitation was not applied until the respiratory movements had nearly ceased. The effect is to produce complete arrest of the heart, which, however, shows a beginning of escape from the arrest after the lapse of about a minute, and 20 seconds later resumes beating slowly and feebly, and with but little effect upon the blood-pressure. Respirations are not resumed spontaneously, but the animal was recovered 5 minutes after the respirations had ceased, by artificial respiration (compression of thorax) continued during about 2 minutes. The first signal mark shows the period of strong chloroform administration: the second that of vagus stimulation.

chloroform *plus* artificial vagus excitation on the other, shows conclusively that in the former case, as in the latter, the actual cause of the arrest of the heart (and of the

FIG. 14.—Tracing showing the effect upon the heart (1) of weak and (2) of stronger vagus excitation during extreme chloroform anæsthesia. The first signal mark shows the period of strong chloroform administration: the second that of weak vagus stimulation: the third that of stronger vagus stimulation. The chloroform was given until the respiration had ceased and the blood-pressure had fallen to 20 mm. Hg. Excitation of the vagus by induction shocks of very moderate strength produced only a momentary arrest of the heart, but stronger excitation caused instant and permanent arrest.

respiration as a secondary effect) is inhibition excited through the vagus. Thus figs. 5, 6, 7, and 15 show such a cardiac and respiratory arrest produced by strong chloroform alone, and figs. 12, 13, and 14 the same phenomenon produced under varying degrees of chloroform anæsthesia by vagal stimulation. In figs. 12 and 13 it is seen that the ventricle has escaped from the inhibition and has resumed contraction

* *Op. cit.*

with an independent (slower) rhythm. In all such cases as these recovery may be effected if artificial respiration be started soon (fig. 15), before the respiratory centre has been allowed to remain too long under the influence of the chloroform *plus* anæmia; or if the anæsthetisation be not very deep, there may be spontaneous recovery (fig. 12). In other cases the ventricle does not escape spontaneously (fig. 14); but it may be caused to contract by rhythmic compression through the chest wall (fig. 15). The arrest of the heart (and, secondarily, of the respiration) is due therefore to an excitation by chloroform of the cardio-inhibitory centre.* Arloing showed that it does not occur with cut vagi, and this is also emphasised by Embley; moreover, it does not occur if a small dose of atropine has been previously given (see below, p. 328), and it may also fail to be apparent after prolonged anæsthetisation with chloroform in moderate dosage. It fails to occur also in certain individuals, which seem to be less susceptible than others to the cardio-inhibitory effects of the drug. Instances are shown in fig. 22, A, and

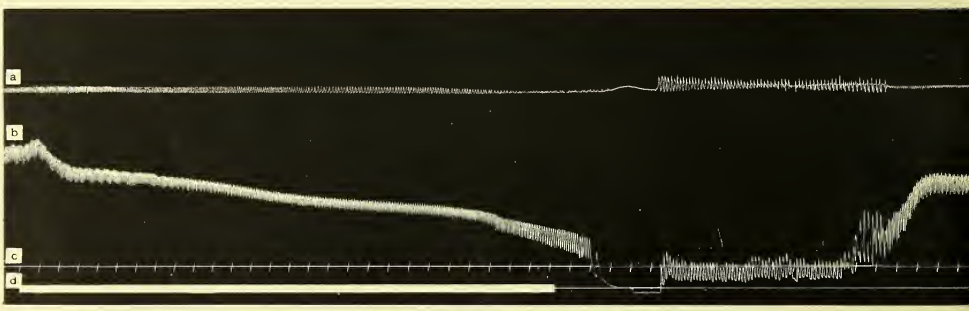

Fig. 15.—Tracing showing (secondary) inhibition of heart from strong chloroform inhalation, with simultaneous cessation of respiration. Recovery, after 30 seconds' arrest, by means of artificial respiration effected by chest compression.
a, respiration; *b*, arterial pressure; *c*, time in 10 seconds; *d*, signal line (2 mm. above abscissa of blood-pressure).

also in fig. 16; the latter from a dog in which the inhalation of air strongly charged with chloroform vapour was pushed until respirations had ceased, the heart continuing to beat with great regularity five minutes longer, but during the last three minutes at a slower rate (probably the result of independent ventricular action).

In connection with this subject, we have investigated the effect of vagal excitation upon the heart in different stages of chloroform anæsthesia, and the effect of small doses of atropine upon the result of vagal excitation. In light anæsthesia, an adequate stimulation of the vagus produces, as in absence of anæsthesia, complete arrest of cardiac movements with a fall of blood-pressure to zero. But even if the excitation be continued, this condition does not last, for although the auricles may

* The above tracings make it abundantly evident that the assertion of Lawrie (*Lancet*, 1890, vol. i. p. 1393), founded on the report of the Hyderabad Commission, "that sudden death from stoppage of the heart is not a risk of chloroform itself," is completely erroneous.

remain quiescent, the ventricles escape from the inhibition and resume contracting, at first very slowly, afterwards more quickly, although often somewhat irregularly, so that the blood-pressure again rises. On ceasing to excite the vagus, the heart beats more rapidly and more strongly, and there may be a temporary rise of blood-pressure above the normal average just before the excitation. This characteristic effect is shown in fig. 18.

In chloroform anæsthesia the effect upon the heart of vagal excitation is more pronounced and permanent.* The complete arrest of cardiac action may last long enough to cause a concomitant arrest of respiration, and when this occurs, even if the

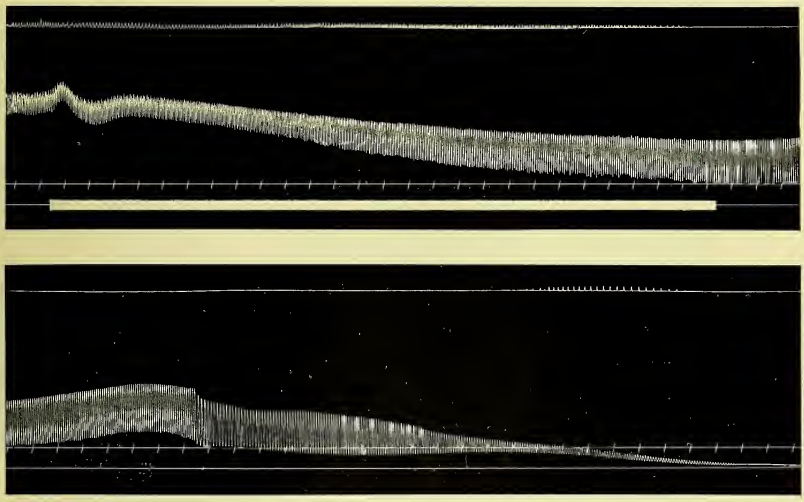

Fig. 16.—Shows a tracing of respiration and blood-pressure under inhalation of air strongly charged with chloroform vapour. This tracing illustrates the type of result obtained when cardiac inhibition does not occur to the extent of causing complete arrest of the heart, but merely a slowing (which may be suddenly increased), the heart failing quite gradually. The chloroform inhalation lasted 4½ minutes, at the end of which period respiration had ceased, and was not again renewed until the heart had nearly stopped, when a 'staircase' group of 25 slow gasping respirations showed themselves—the so-called 'respirations of the death-agony.' The lid reflex, which was present immediately before the inhalation began, disappeared within one minute.

ventricles resume action, their rhythm is very slow, and their force insufficient to raise the blood-pressure much, so that, as a rule, respirations are not spontaneously resumed although artificial respiration may effect recovery. Or it may happen, especially with a strong excitation, that the recovery of the ventricles does not occur at all, and even heart massage, which can be effected by compressing the chest, to which the ventricle may at first respond, may be incapable of causing it permanently to resume its action.

* Dastre states that this increase of vagal excitability under chloroform was first noted by Vulpian (*C. r. Soc. Biol.*, 1883, p. 243). According to François-Franck (*ibid.*, p. 255), it disappears with increase of anæsthesia, but this is not in accordance with our experience so far as concerns direct excitation.

If the chloroform be pushed until respirations cease altogether and the blood-pressure is reduced to a few millimetres of mercury, the only sign of life being the slow beat of the heart, adequate vagal excitation will still cause inhibition, which under these circumstances lasts as long as the excitation; the removal of excitation being immediately followed by a resumption of the slow, weak beats. Such inhibition can be obtained as long as there is any perceptible beat (fig. 17).

We have also re-studied the effect and dosage of atropine in preventing inhibition through the vagus. The results obtained are illustrated in the tracings reproduced in fig. 19. (See also fig. 10 for its effect on reflex vagal excitation.)

If a dose of sulphate of atropine of 0·00002 gramme per kilo. be given hypodermically in the dog, the effect upon the vagus is manifest about fifteen to twenty minutes

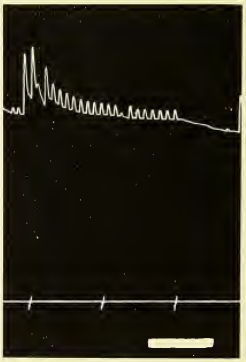

FIG. 17.—Effect of moderate vagal stimulation in the last stage of chloroform anæsthesia, the respiration having long ceased, and the heart beating slowly, feebly, and irregularly. The signal marks the period of vagal stimulation. (The alignment of the signal is a little too much to the left.) It will be seen that excitation of the peripheral vagus still causes arrest of cardiac action, which is at this stage probably entirely ventricular.

after administration, and lasts about three hours. The result of such a dose is in some cases to abolish for a time all vagal influence upon the heart (fig. 19, I.). But in most cases, although there is not complete abolition, nevertheless the strongest vagal excitation is unable to produce, in any stage of chloroform anæsthesia, complete cardiac arrest (fig. 19, II. to VI.). There may be, even with comparatively weak excitation, a slowing of the heart and a consequent fall of blood-pressure; but it is no greater with strong than with weak excitation, and is never accompanied by respiratory arrest, unless in using a very strong excitation there is escape of current to the central end of the nerve. This peculiar condition, in which vagal excitation is unable to cause arrest, but only slowing and diminution in force of the heart, persists for nearly three hours, the

slowing becoming as time proceeds gradually more marked, and the consequent fall of blood-pressure lower. But cardiac arrest does not show itself until the influence of the atropine has completely passed, and the former conditions can be then restored by a similar dose.

There is no reason to believe that the human subject is less susceptible to the influence of atropine than the dog, and the opinion which has been expressed, that an enormous dose would be required to abolish the power of the vagus to cause cardiac arrest, appears therefore to be erroneous.*

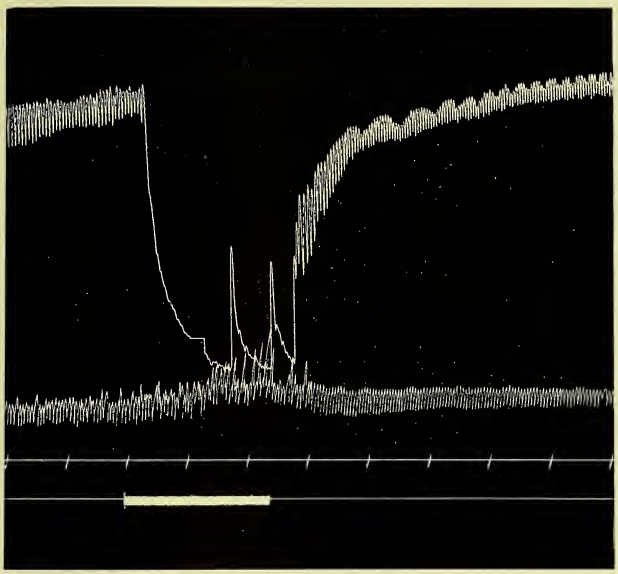

FIG. 18.—Normal effect, in the dog, of vagus stimulation of moderate strength (coil 100 mm.) with light anæsthesia, showing the tendency of the heart to escape from the inhibition. This was taken immediately before and from the same dog as the (reduced) tracings shown in figs. 12, 13, and 14, but chloroform was administered in the interval, and the tendency to inhibition is seen in these to be much more pronounced.

Since abrupt arrest of the heart and of respirations can be absolutely prevented by prior administration of a small dose of atropine, the conclusion forces itself upon us that the precaution of such administration is one that should never be omitted. Atropine cannot, as we shall see, prevent death where a dose of chloroform sufficient to produce paralysis of respiration and complete "paralytic dilatation" of

* See on this subject remarks by H. C. CROUCH and T. G. BRODIE in *Trans. Soc. Anæsth.*, vol. vi. pp. 70 and 81, 1904. J. HARLEY (*Brit. Med. Journ.*, vol. ii., 1868, p. 320) recommended a dose of from $\frac{1}{100}$ grain to $\frac{1}{40}$ grain in man, DASTRE (*Soc. Biol.*, 1883, p. 242) states that a dose of atropine amounting to 0·0015 gramme ($=\frac{1}{43}$ grain) is sufficient for the purpose indicated. LANGLOIS and MAURANGE (*Arch. de Phys.*, 1895, p. 692) recommend the employment of oxy-sparteine in place of atropine.

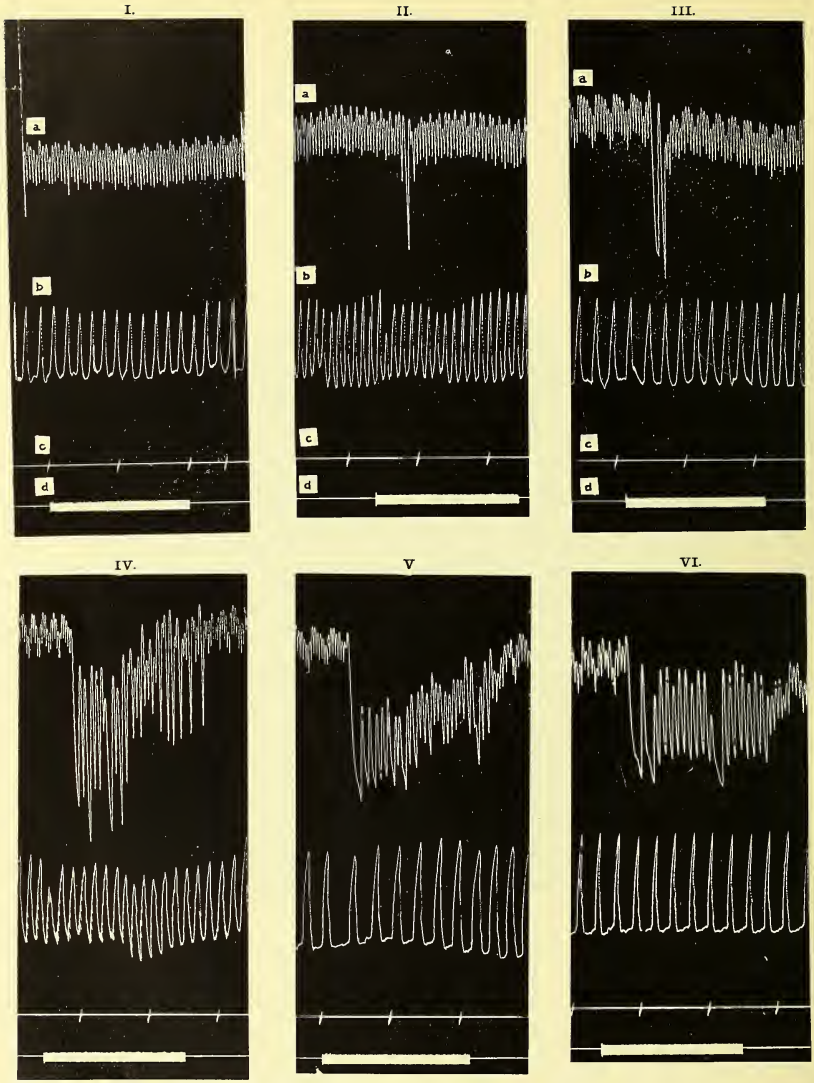

FIG. 19.—Tracings to illustrate the influence on cardiac inhibition by vagus excitation of a small dose of atropine sulphate (·00054 gramme = $\frac{1}{120}$ gr.) administered to a dog weighing 28 kilog. = 61½ lbs.

I., tracing taken 15 minutes after the atropine was administered by injection into the pleural cavity; II., 30 minutes after; III., 45 minutes; IV., 1 hour; V., 1½ hours; VI., 2½ hours after administration.

The blood-pressure and extent of anæsthetisation are approximately the same in all.

The strength of stimulus was the same in all, and was adequate to produce strong inhibition in the absence of atropine. Note that this effect is abolished in 15 minutes, and does not reappear in the same form and extent during at least 2½ hours, although there is a gradually increasing amount of inhibition shown as the atropine is becoming eliminated. But even 2½ hours after the injection the strongest stimulus (coil at 0) failed to produce any more effect than that shown in VI.

a, blood-pressure curve; *b*, respirations; *c*, time in 10 secs.; *d*, signal showing period of vagal excitation.

the heart has been administered, but this is a condition which no anæsthetist has any right or occasion to produce. On the other hand, it can prevent the sudden cardiac arrest which may show itself even at a comparatively early stage of chloroformisation, and which may be produced by the drug itself acting on the cardio-inhibitory centre, with (or without) the assistance of an effect reflexly produced upon that centre by the operation which is proceeding; or by some other concomitant, such as the incidental occurrence of dyspnœa, which is well known also to cause inhibition through the vagus.*

Whether the vagi be cut or their terminal branches blocked by atropine, or whether they be left intact, the ultimate effect of chloroform upon the heart, if its inhalation be pushed, is to produce complete arrest in diastole, a condition being observed which has been termed "paralytic dilatation." The condition is a peculiar one, for the cardiac muscle is not only paralysed and incapable of contracting spontaneously, but is in a *permanently refractory condition*, and incapable of responding to stimuli of any sort.†

To all forms of direct stimulation the heart gives no response, although the muscular tissue is not dead, and it suffices to remove the chloroform by producing a flow of unpoisoned blood or circulating fluid through the coronary vessels to restore its rhythmic contractility and its power of responding to artificial stimuli.‡ This shows that the refractory condition is due to the influence of the drug upon the heart, and it is commonly assumed by writers upon the subject that chloroform enters into combination with the contractile substance of the cardiac muscle and thereby deprives it of irritability. That this assumption is not justified is clear from the fact that no such effect—in doses which are more than sufficient to paralyse the heart—is produced upon either skeletal or upon plain muscular tissue. It is impossible to believe that the chemical constitution of these forms of contractile tissue is so different from that of heart muscle, that the one combines with chloroform and is thereby rendered devoid of irritability, whilst the others show no tendency to combine with or to be materially affected by the drug. It is much more probable that the effect produced is one of excitation of the terminations of the inhibitory nerves, the heart being thereby rendered irresponsive to stimuli. The argument that may be urged against this hypothesis, that if this were so the effect of chloroform in paralysing the heart would be prevented by atropine, is met by the statement that, although atropine blocks the

* An instance of the last-named complication is illustrated in fig. 20. In this animal the breathing was laboured, owing to obstruction of the air-tubes by mucus. There was marked dyspnœa, and the heart-beats were very slow and even arrested whenever the dyspnœa became intense. The violent respiratory efforts succeeded from time to time in clearing the air-passages, and this was followed by partial recovery. This pronounced inhibition was due to asphyxia, which, if more marked than in the instance given, may lead to entire arrest of the heart. Such inhibition from asphyxia does not occur with cut vagi. The condition is one which is not unfamiliar to anæsthetists, who are cognisant of its cause and danger. It is not liable to occur if a prior dose of atropine be administered, partly on account of the effect of this on the vagi and also because atropine tends to prevent the secretion of the mucus which causes the obstruction to respiration. This reason for the administration of atropine will apply equally to ether as to chloroform anæsthesia.

† Sherrington and Sowton (*op. cit.*), in the isolated and perfused cat's heart arrested by chloroform, obtained a renewal of the contractions on stimulation of accelerator nerves. But it is doubtful if this could be obtained with a strong dose of chloroform.

‡ Sherrington and Sowton.

inhibitory path, there is no conclusive evidence that it acts upon the inhibitory end-apparatus in the muscular fibres. According to this view the chloroform-heart—provided that the dose is insufficient to kill the contractile tissues generally—is in a condition of active inhibition rather than in one of passive paralysis. In support of this, it may be stated that although, if the chest be opened immediately after death, the heart may be completely irresponsive to all forms of stimuli, after a little while it often happens that it begins to respond and even exhibits feeble spontaneous contraction,

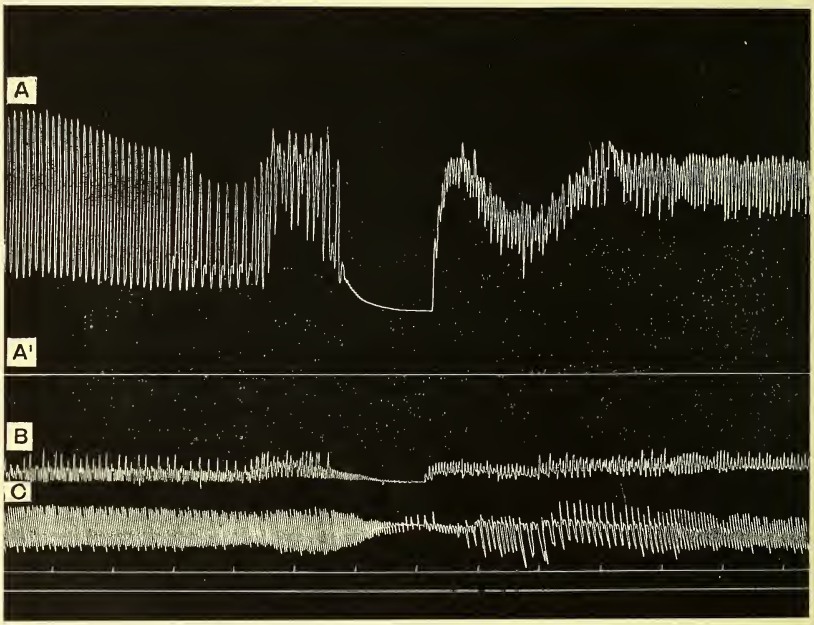

FIG. 20.—Cardiac inhibition produced during chloroform inhalation by dyspnœa resulting from accumulation of mucus in air-passages.

A, blood-pressure; A^1, line 1 centimetre below the zero of blood-pressure; B, costal respiration: C, diaphragmatic respiration. The dyspnœic condition is shown by the extreme rapidity of the respiratory movements at the left hand of tracing. About the middle of the tracing the obstruction to the passage of air was removed, and with the disappearance of the dyspnœa the heart resumed its normal rate of rhythm.

although the chloroform has not been washed away. The phenomenon may be explained if we assume that the inhibitory end-apparatus has died before the contractile substance of the muscular fibres.

To sum up this part of the subject, the conclusions which it appears justifiable to draw regarding the causation of death from the effect of chloroform upon the heart are as follows:—(1) Death *may* be caused in the earliest stage of administration by the action of the drug upon the cardio-inhibitory centre, the stimulation being reflex.

For convenience of description, this may be termed "primary" inhibition. It is probable that it occurs but rarely in man, and some altogether deny that it can produce a fatal result; it is, however, impossible to explain the well-authenticated instances of sudden heart failure at the very commencement of administration without assuming that under certain conditions such primary inhibition, which, when it occurs in other cases, is usually quite evanescent, is occasionally persistent and fatal.*

(2) At a somewhat later stage of administration death is liable to occur from sudden heart failure due to inhibition produced by the action of the drug on the cardio-inhibitory centre, aided by its action on the neuro-muscular end-apparatus of the heart itself, and also by increasing venosity of blood caused by failing respiration. The liability to this form of inhibition, which may be termed "secondary" (as well as to that mentioned under 1), can be removed by the prior exhibition of a moderate dose of atropine, which, by diminishing or abolishing the effect upon the heart of excitation of the cardio-inhibitory centre by chloroform, deprives it of the power to produce sudden cardiac arrest. This precautionary measure was long ago suggested,† and all recent work on the subject emphasises the importance of its adoption.

That the prolonged administration of chloroform itself tends to diminish its excitatory effect upon the cardio-inhibitory centre in the medulla oblongata is probable from the fact that a dosage of chloroform can be given with impunity at the later stages of a long operation which would be highly dangerous if given at earlier stages.

The respiration in these "secondary" cases of inhibition may stop simultaneously with, or shortly before, or immediately after the heart. We have frequently succeeded in effecting resuscitation by artificial respiration in animals, in which both heart and respiration had completely stopped at this stage of poisoning after even a minute or two of cessation of heart-beats, and in two cases as long as three and five minutes respectively after complete cessation; but in other instances we have failed to obtain recovery after three minutes or more of cessation.

The two cases just referred to are of exceptional interest. In the one the animal had been under ether for about an hour (the anæsthetic being inhaled through a Y-shaped trachea tube), when chloroform, at first with considerable intermixture of air, was substituted for the ether. The effect was to produce a gradual fall of blood-pressure from 100 mm. Hg. to about 40 mm., after which both it and the respiration, which was much shallower than under ether, remained nearly constant. After five minutes the lateral air-inlet was cut off, and the dog received a much stronger dose of chloroform. The result of this was immediately apparent in a further fall of blood-pressure, and a slowing and irregularity of the respirations, which ceased altogether about two minutes later, although the heart continued to beat regularly and the blood-pressure was maintained and even rose slightly. About one minute twenty seconds after cessation of respiration the heart suddenly

* This mode of producing inhibition has been especially emphasised by ARLOING (*Thèse, Paris*, 1879), who describes the effect of chloroform in producing heart failure in terms very similar to those which we have employed.

† PITHA (1861, quoted by DASTRE); J. HARLEY, *Brit. Med. Journ.*, vol. i., 1868, p. 320; SCHÄFER, *Brit. Med. Journ.*, vol. ii., 1880, p. 620. FRASER (*Brit. Med. Journ.*, vol. ii., 1880, p. 715), BROWN-SÉQUARD (*C. r. Soc. Biol.*, 1883, p. 289), and DASTRE and MORAT (*Lyon Méd.*, 1882, and *C. r. Soc. Biol.*, 1883, pp. 242 and 259) have made a similar recommendation, but have suggested the addition of morphia, and this combination has often been used (first systematically by AUBERT, *C. r. Soc. Biol.*, 1883, p. 626). But morphia is in some ways antagonistic to atropine, and tends by itself to exalt the irritability of the cardio-inhibitory centre. Without atropine it would undoubtedly increase the danger of heart-arrest in chloroform administration.

stopped and the blood-pressure fell to zero. Artificial respiration (by the pump) was now started, and maintained for five minutes, and two injections of 4 c.c. adrenalin chloride (1 per mille) were meanwhile made into the pleural cavity without the least result being apparent, the heart remaining quiescent and the blood-pressure at zero the whole time. Intermittent compression of the thorax was now substituted for perflation, and the heart responded to this by a pulsation with each compression, although in the intervals the blood-pressure returned to zero. After continuing the compression for a little over a minute, the heart commenced beating spontaneously and the average blood-pressure rose to 50 mm. Hg. It required, however, another three minutes of artificial respiration before the diaphragm began to act and the intermittent compression could be desisted from for a time; but even then (although no more chloroform had been inhaled) the respirations again gradually failed and ceased after ten minutes. A second spell of intermittent compression, lasting two minutes, now, however, effected complete restoration. When this was established and the lid reflex had become brisk, the blood-pressure being 110 mm. Hg., chloroform was again administered in strong form. The blood-pressure gradually fell. In two minutes the lid reflex had disappeared, and in another minute respirations had ceased, followed in twenty seconds by complete cessation of heart beat. Five minutes was now allowed to elapse, during which the animal was to all appearance dead. Artificial respiration by chest compression was then recommenced, and two more doses of 3 c.c. adrenalin chloride solution were successively injected. Five minutes after the artificial respiration was commenced and immediately after the final dose of adrenalin, the heart began to beat spontaneously, and the blood-pressure, at first very low, gradually rose in about four or five minutes, during which artificial respiration was maintained, to about 100 mm. Hg. Natural respiration was, however, not again resumed, the medulla oblongata having to all appearance been deprived for too long a time in this instance of blood.

In the second dog a lethal dose of chloroform vapour was administered twice. The first time both heart and respiration (the latter ten seconds before the heart) had stopped after three and a half minutes' administration. Half a minute later the chloroform was removed, and 4 c.c. of 1 per 1000 adrenalin chloride solution was injected into the pleural cavity. This produced no apparent effect. Three minutes after cessation of heart and respiration, chest compression was begun. Each compression produced a heart response, and the blood-pressure rose from zero to a few millimetres. After four minutes' chest compression another similar dose of adrenalin was injected into the pleural cavity, chest compression being continued. The blood-pressure then began to recover, the heart now beating slightly more rapidly than the chest compression, but natural respiration (diaphragm) was not resumed until another six minutes had elapsed. As in the last case, however, the natural respirations gradually became shallower and slower again, although no more chloroform was given, and fifteen minutes later ceased altogether, the heart and blood-pressure also becoming weak and low; the administration at this stage of a decoction of pituitary, and later of another dose of adrenalin, with the idea of restoring the heart's action, produced no visible effect. After two minutes' cessation of respiration (the heart still beating feebly), recourse was again had to chest compression and then to artificial respiration by the pump. This was very soon followed by recovery of heart and blood-pressure, and a few minutes later natural respirations were resumed and maintained, and artificial respiration was discontinued; recovery was, in fact, complete.

(3) In late stages of administration the heart is paralysed by the direct effect of the drug, acting either upon its muscular tissue (as is usually assumed), or (as we believe) by exciting the neuro-muscular inhibitory end-apparatus, and through this rendering the muscular tissue non-excitable. This effect can probably only occur with a considerable dosage of chloroform in the blood, and the respiratory centre is invariably first paralysed, so that the respirations become slow and shallow and cease before the heart; the time difference between the cessation of heart and respiration being considerably longer than when the cessation occurs early in the administration. This final effect upon the heart is *not* antagonised by atropine. The heart is found to be entirely inexcitable, and no treatment is of any avail short of removal of the poisoned blood from the coronary vessels and the substitution of blood free from chloroform. It is conceivable that this substitution might be done by heart massage, or even by com-

pression of the thorax in attempting artificial respiration; and, as a matter of fact, SCHIFF, BATELLI, and others* have succeeded in restoring the circulation by heart massage combined with artificial respiration (both in dogs and cats, and in one or two rare cases in the human subject), even although a considerable time (fifteen to twenty minutes) had elapsed after complete cessation of the circulation. We ourselves have not succeeded in restoring an animal after the condition here described appeared to be fully established, and we should be disposed to regard the possibility of resuscitation in such cases as remote.†

ANTAGONISING AGENTS.

(1) *Atropine.*—It is apparent from the results obtained by other experimenters, as well as from our own observations, that the chief danger to be guarded against in the administration of chloroform is the inhibitory influence which it produces upon the heart. As we have already pointed out (pp. 328, 329), this influence can be in great measure controlled by the prior administration of a moderate dose of atropine, at least in so far as the primary and secondary instances of inhibition are concerned, and these are the most dangerous because they are apt to occur without the warning which manifests itself in the case of the final heart paralysis, by the prior arrest of respiration. Atropine is therefore to be placed first in the list of antagonising agents; a dose of $\frac{1}{100}$ gr. to $\frac{1}{50}$ gr. for an average man being administered hypodermically half an hour before the administration of chloroform.

(2) *Adrenalin Chloride.*—The employment of this has been suggested in chloroform poisoning by GOTTLIEB.‡ In the two instances which we have recorded on pp. 333 and 334, which were attended by an entirely unusual measure of success so far as resuscitation after apparent death from chloroform had occurred, we administered successive doses of adrenalin, injected into the pleural cavity, as part of the treatment. These happened to be the first two experiments of the series undertaken by us, and we were led to ascribe much of the success which attended them to the use of this drug, and formed high hopes of the value of its administration in cases of chloroform poisoning. Subsequent experience showed, however, that adrenalin by itself is of little or no avail to restore a heart paralysed by chloroform, and even in conjunction with other remedial measures—of which the most important is without doubt artificial respiration by chest compression—we are not in a position, as the result of a number of trials, to affirm that it is able materially to contribute to the process of resuscitation.

(3) *Ammonia Vapour.*—RINGER§ first showed that in the frog's heart ammonia acts as a direct antagonist to chloroform, and may even set in activity a heart which has

* For references see M. BOURCART, *Rev. méd. de la Suisse Romande*, October 20, 1903.

† This is no doubt the condition referred to by RICHET (*Dict. de physiol.*, article "Anesthésie," 1895, p. 523) when he avers that when cardiac syncope occurs artificial respiration never succeeds in effecting restoration; for the statement does not apply to the syncope caused by the secondary inhibition previously referred to.

‡ *Arch. f. Path. u. Pharm.*, Bd. 37, p. 98, 1896. See also BIEDL, *Wien. klin. Wochenschr.*, 1896.

§ *Practitioner*, vol. xxvi. p. 436, 1881.

been arrested by chloroform; and since it also has a stimulating action on the heart and respiratory centre, it is likely that it may prove useful as a restorative in cases in which the pulse and breathing have not altogether ceased. We have investigated the effect in dogs of causing them to inhale a mixture of chloroform vapour and ammonia, made either by dropping chloroform and ammonia upon the cotton-wool of the inhaling bottle, or by mixing chloroform in definite proportions with alcoholic ammonia, using for this purpose a solution of ammonia in absolute alcohol containing 6·8 per cent. of

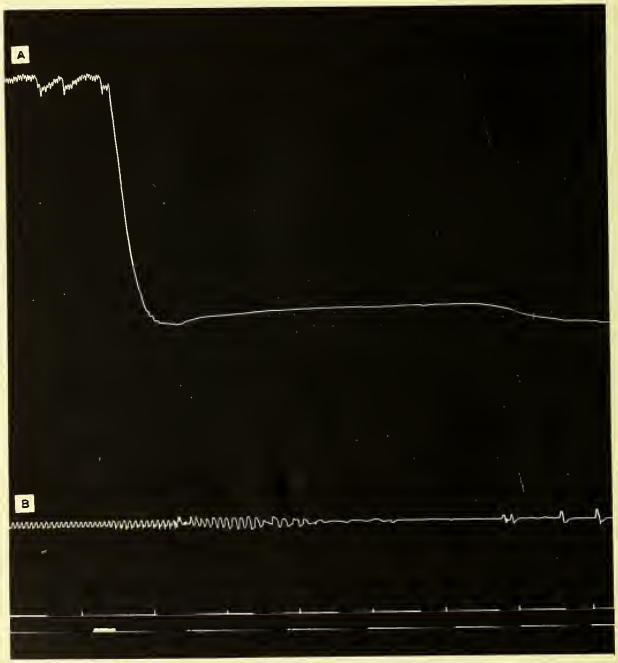

Fig. 21.— Instantaneous heart failure caused by inhalation, at the moment marked by the signal, of air charged with vapour from a mixture of 20 c.c. chloroform and 5 c.c. ammoniated alcohol.

A, blood pressure; B, respirations. The latter continued to show themselves at a slow rate for 3 minutes after the heart had stopped.

ammonia, prepared for us by Messrs Duncan & Flockhart. A mixture of chloroform and ammonia vapours, even if it contain a comparatively small proportion of ammonia, is too pungent to be administered in the first instance, the irritation it causes to the sensory nerves of the mucous surfaces rendering it practically irrespirable. And if the proportion of ammonia be considerable, this excitation may result in powerful cardiac inhibition, and the heart may instantly and permanently stop (fig. 21). If, however,

the proportion of ammonia be less and the animal be already completely under the influence of an anæsthetic, the effect of the addition of the vapour of ammonia or ammoniated alcohol to the chloroform inhaled is strikingly beneficial. The blood-pressure falls but slightly even during a prolonged period of inhalation—the strength of the heart is well maintained—and the tendency to failure of respiration, which is so marked a feature

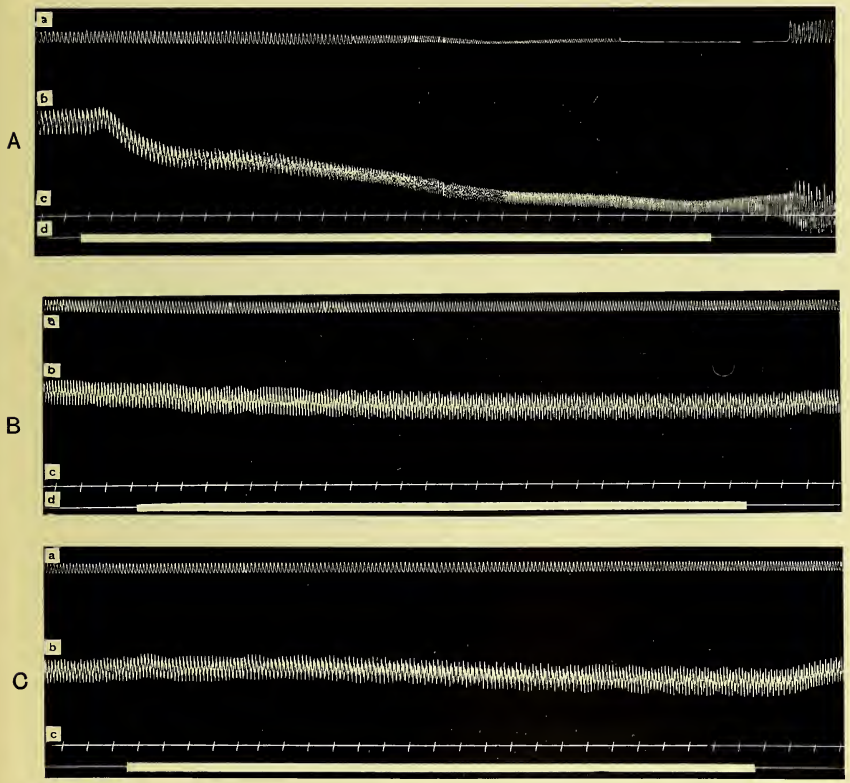

FIG. 22.—Tracings showing in a comparative manner in the same animal the difference of effect between inhalation (A) of pure chloroform, (B) of a mixture of chloroform with ammoniated alcohol (9 to 1), and (C) of a mixture of chloroform and absolute alcohol (9 to 1).

Note in A the rapid fall of blood-pressure and the speedy failure of respiration; in this case the heart continued to beat after the respirations had ceased. After a respiratory arrest of more than a minute, during which the heart showed strong tendency to inhibition, artificial respiration by chest compression was resorted to (the beginning of this is shown): in rather more than a minute the blood-pressure rose—the natural respirations were then resumed. Note in B and C the very slow and slight fall of blood-pressure, and the complete maintenance of respiration during the whole time of administration. In all three cases the air of respiration was charged as strongly as possible, at the ordinary temperature of the laboratory, with the vapour to be inhaled.

a, respirations; *b*, blood-pressure; *c*, time in 10 secs.; *d*, signal showing period of administration. In all cases there was distinct corneal reflex immediately prior to the administration, and this disappeared within 1 minute.

of strong chloroform inhalation, is considerably diminished. The comparative effects of inhalation of chloroform alone and of chloroform *plus* ammoniated alcohol are shown in the tracings A and B reproduced in fig. 22, and the beneficial results of substituting a mixture of chloroform containing alcoholic ammonia for pure chloroform are illustrated in the tracing given in fig. 23.*

(4) *Alcohol Vapour.*—In order to determine how much of the beneficial effect of the mixture of alcoholic ammonia with chloroform was due to the alcohol used as a

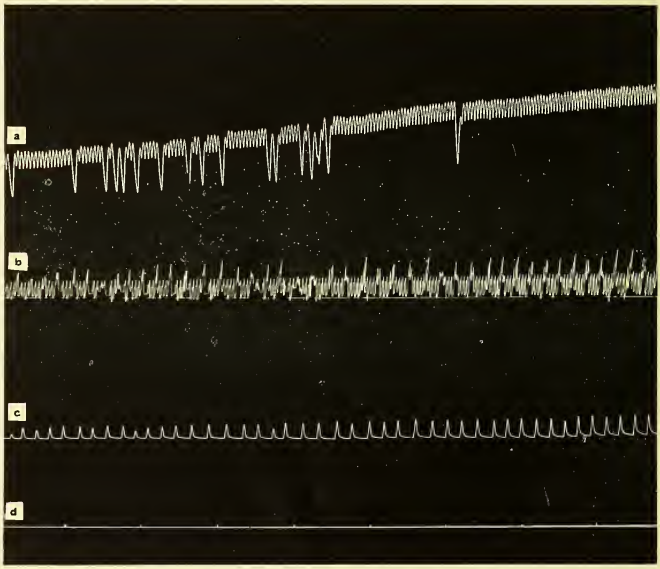

FIG. 23.—Beneficial effect upon blood-pressure, heart, and respiration of substituting ammoniated alcohol and chloroform (1 to 9) for the pure chloroform which was being administered to a dog.

a, blood-pressure ; *b*, heart-beats, recorded by a needle passed through chest wall ; *c*, respiration ; *d*, time in 10 secs. Notice the increasing strength of the heart-beats and of the respiratory movements.

It is also seen that the dropped heart-beats due to vagal inhibition which were occurring during chloroform alone gradually disappear as the result of adding ammoniated alcohol to the chloroform.

vehicle for the ammonia, we next proceeded to investigate the results of using for inhalation the vapour given off from mixtures of chloroform and alcohol. We were somewhat surprised to find that the results were nearly as beneficial when alcohol alone was used, as when alcoholic ammonia vapour was employed. The difference between the effect produced upon blood-pressure and respiration by inhalation of pure chloroform in the one case, and by inhalation of a mixture of chloroform containing 1 part in 10

* The addition of ammonia gas to the chloroform to be used for inhalation was advocated by J. DUNCAN MENZIES (*Brit. Med. Jour.*, vol. ii., 1895, p. 871).

by volume of absolute alcohol, is exemplified in fig. 22 (A and C). It will be observed that the effect of the addition of 1 part absolute alcohol to 9 parts chloroform is to largely prevent the fall of blood-pressure, which is recognised as being one of the most serious dangers attendant on chloroform inhalation, and at the same time to maintain the respirations at a force and frequency very little less than normal. The administration was made in both cases on the same animal by the same method, and using the same quantities of the solutions.

It may also be observed how much more readily recovery takes place after removal of the mixed vapour than after removal of the chloroform. On the other hand, disappearance of the lid reflex occurs a little sooner when pure chloroform is used, but the difference is not great.

We have tried other proportions of alcohol and chloroform, but have obtained no

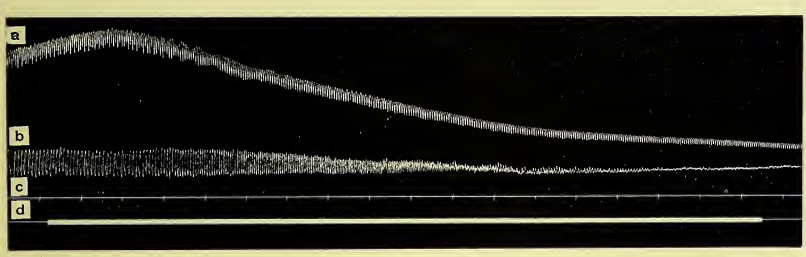

Fig. 24.—Administration by inhalation of air strongly charged with pure chloroform during 3 minutes to dog weighing 11 kilog. which had received (1½ hr. and 1¾ hr. previously) two doses of ·00027 g. ($\frac{1}{170}$ gr. in all) atropine sulphate. The vagus, tested immediately before this tracing was taken, gave no slowing and only a slight fall of pressure, even with coil at 0.

Notice (1) the preliminary rise of blood-pressure due to excitation of vasomotor centre, succeeded by (2) a rapid and regular fall, less steep towards the end; (3) entire absence of slowing of pulse; (4) increase of rapidity, but decrease of excursion of respiratory movements, which became irregular, and eventually hardly perceptible.

a, blood-pressure curve; *b*, respirations; *c*, time in 10 secs.; *d*, signal of chloroformisation and abscissa of blood-pressure. The heart was still beating 4 minutes later, but the blood-pressure was at zero, and the respirations had wholly ceased. The animal was then subjected to artificial respiration by chest compression, and in 1 m. 40 secs. natural respirations were resumed, and the heart and blood-pressure rapidly recovered. The tracing shown in the next figure was taken prior to this one.

better results. Indeed, with a 20 per cent. alcohol chloroform the respirations appeared to be more affected than with the 10 per cent. mixture.

The beneficial effect can hardly be due to the mere dilution of the chloroform vapour by alcohol vapour; moreover, dilution with ether has not this effect, but the result is then practically the same as is obtained with undiluted chloroform. It is therefore to be ascribed directly to the beneficial action of the alcohol on the heart and respiratory centre. We are of opinion that a mixture containing one part by volume of absolute alcohol to nine parts of chloroform should be used when chloroform is indicated as the anæsthetic, since these results show that it is far safer in its action than pure chloroform. There seems reason to believe that the greater safety of the A.C.E. mixture over chloroform depends upon the alcohol it contains, and that the ether is unnecessary; it may further be noted that the alcohol in this mixture is in needlessly

large proportion.* The beneficial effect of adding absolute alcohol to the chloroform used for inhalation is seen in atropinised as well as in normal animals. The respective effects of administering pure chloroform, on the one hand, and chloroform containing 10 parts per cent. of absolute alcohol, on the other, to a dog weighing 24 lbs., which had previously received two successive doses of ·00027 gramme of atropine sulphate, are illustrated by the tracings shown in figs. 24 and 25.

A mixture which is frequently used by anæsthetists in place of the A.C.E. is one of ether and chloroform without alcohol; but from the facts here put forward it would seem better rather to omit the ether than the alcohol. This remark is not to be understood as implying that ether by itself is not a safe anæsthetic—far safer than chloroform, however diluted—but merely that it has not the same antagonising influence as alcohol upon the dangerous tendencies of chloroform.

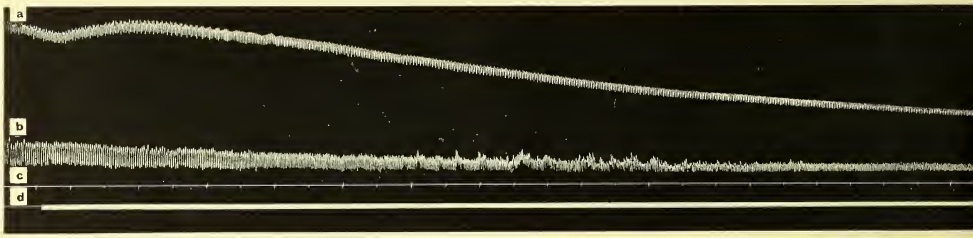

FIG. 25.—Tracing showing the effect of the inhalation of air strongly charged with the vapour from a mixture of 9 parts pure chloroform and 1 part absolute alcohol. The inhalation was continued during nearly 5 minutes. The tracing was begun 10 minutes before that shown in the preceding figure, and is from the same animal (under the influence of atropine sulphate). Notice, as compared with fig. 24, (1) the much more gradual fall of blood-pressure, which even after nearly 5 minutes of administration still keeps fairly high, (2) the effect on the respirations, which are far less influenced than by the pure chloroform, being well maintained during the whole time. On desisting from the inhalation, recovery of blood-pressure was rapid, and the lid reflex, which had disappeared early during the inhalation, was brisk 5 minutes after the chloroform and alcohol mixture had been removed.

a, blood-pressure; *b*, respiration; *c*, time in 10 secs.; *d*, signal.

POST-MORTEM CONDITIONS AFTER DEATH FROM CHLOROFORM.

Although these conditions have been often described, it may not be out of place to add our own experience and observations.

Heart.—In all the cases which we examined immediately after death, all the cavities—with, sometimes, an exception for the left auricle—were distended with blood, the right auricle and great veins of the thorax enormously so. The left ventricle always contained a considerable quantity of blood, but rather less than the right ventricle. If, however, the examination were made some little time after death, the left ventricle was always found empty and firmly contracted. This change from the full flaccid condition to the empty firm condition took place in one case within twenty minutes, while in others it did not show itself for forty-five minutes.

* *Cf.* on this subject, QUINQUARD, *C. r. Soc. Biol.*, 1883, p. 425; and DUBOIS, *ibid.*, p. 441.

Lungs.—The pulmonary arteries are greatly distended with blood. Otherwise the lungs usually present a perfectly normal appearance externally. But in cutting them open we found, in six out of twenty cases examined, a considerable amount of frothy mucus in the bronchial tubes.

Abdominal Viscera.—These exhibited marked venous congestion, especially well seen in the liver, which may be greatly swollen and project beyond the thoracic cage.* It is thus exposed to some risk of rupture if artificial respiration be attempted by the Howard method. This happened in one of our cases, although we were aware of the danger, and always endeavoured to avoid it by compressing the chest well above the liver.

All these appearances are very similar to those which result from asphyxia due to deprivation of air, whether caused by drowning or otherwise. But they are produced independently of any asphyxia caused by paralysis of the respiration by the drug, for they show themselves equally when artificial respiration has been maintained by perflation, and the drug has produced death solely by its action on the heart. Nevertheless, the ultimate effect upon the heart of chloroform and of deprivation of air respectively is strikingly similar. In both cases the final result is a condition of "paralytic dilatation," or, as we have preferred to term it, "inhibition paralysis," in which the heart is absolutely refractory to all kinds of stimuli. In the case of chloroform the exciting cause is doubtless the drug itself; in the case of asphyxia, it is probably the carbon dioxide which has accumulated in the blood and tissues.†

* To observe this condition of the liver and abdominal organs, it is necessary to open the abdomen before the thorax. For if the contents of the latter be first laid bare, and any of the great veins injured, the congestion of the abdominal viscera at once subsides, owing to the escape of blood from their vessels.

† *Cf.* on this subject the Report of the Committee on Suspended Animation, *Trans. Med. Chir. Soc.*, 1904, Suppl., p. 63.